

## REMARKS

In the present communication, claims 1 and 5 have been amended; claims 11-13 have been canceled; and no claims have been added. The amendments do not include new matter and are fully supported by the specification and claims as filed. Accordingly, upon entry of the present amendment, claims 1-3, 5-6 and 8-10 will be under consideration.

### Rejections under 35 U.S.C. §103

Applicant respectfully traverses the rejection of claims 1-3, 5, 6 and 8-13 under 35 U.S.C. §103(a) as allegedly obvious over Nurminskaya et al., in view Hashimoto et al. and Oliverio et al., further in view of Heyninck et al. and Grey et al. The recent U.S. Supreme Court decision in the *KSR International v. Teleflex Inc.* (82 USPQ2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

With regard to claims 1-3, directed to a method for suppressing pathological calcification, without acquiescing to the rationale presented in the Office Action, and in order to expedite prosecution of the instant application, Applicant has amended claim 1 by deleting inhibitor A20. As amended the claim recites "a method for suppressing pathological calcification of the meniscal and articular cartilage matrix in a subject in need thereof, comprising: administering to the subject an inhibitor of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix, wherein the inhibitor is NG-

monomethyl-L-arginine acetate (NMMA), thereby suppressing pathological calcification in the cartilage matrix in the subject.”

Applicant respectfully submits that the Office Action fails to present a *prima facie* case of obviousness as to the claims as amended because the cited references, whether considered individually or taken as a whole, fail to teach or suggest the invention of the claims as amended. Applicant submits that the cited references fail to teach use of NG-monomethyl-L-arginine acetate (NMMA) to suppress pathological calcification of the meniscal and articular cartilage matrix. Further, the cited references fail to teach inhibition of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) by administration of NMMA as claimed. Nurminskaya et al. does not teach administering NMMA to a subject to inhibit activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix to suppress pathological calcification of the meniscal and articular cartilage matrix. The teachings of Hashimoto et al., Oliverio et al., Heyninck et al. and Grey et al. fail to remedy such deficiency because none of the cited references alone or in combination suggest or teach use of NMMA as recited in the claims.

Accordingly, Applicant respectfully requests withdrawal of the rejection.

With regard to claims 5, 6 and 8-10, directed to a method for inhibiting TGase activity of zymogen Factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase) in a chondrocyte, without acquiescing to the rationale presented in the Office Action, and in order to expedite prosecution of the instant application, Applicant has amended claim 1 by deleting inhibitor A20. As amended the claim recites a “method for inhibiting TGase activity of zymogen Factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase) in a chondrocyte, comprising contacting the chondrocyte with an effective amount of an inhibitor of a TNF $\alpha$  receptor-associated signaling factor (TRAF), wherein the inhibitor is NG-monomethyl-L-arginine acetate (NMMA), thereby

In re Application of:  
Robert Terkeltaub  
Application No.: 10/669,540  
Filed: September 23, 2003  
Page 6

PATENT  
Attorney Docket No. UCSD1570-1

inhibiting TGase activity of zymogen Factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase) in the chondrocyte.”

Applicant respectfully submits that the Office Action fails to present a *prima facie* case of obviousness as to the claims as amended because the cited references, whether considered individually or taken as a whole, fail to teach or suggest the invention of the claims as amended. Applicant submits that the cited references fail to teach inhibition of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) by administration of NMMA as claimed. Nurminskaya et al. does not teach administering NMMA to a subject to inhibit activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix to suppress pathological calcification of the meniscal and articular cartilage matrix. The teachings of Hashimoto et al., Oliverio et al., Heyninck et al. and Grey et al. fail to remedy such deficiency because none of the cited references alone or in combination suggest or teach use of NMMA as claimed.

Accordingly, Applicant respectfully requests withdrawal of the rejection.

With regard to claims 11-13, directed to a method for identifying an agent that inhibits matrix calcification, the Office Action relies of the teachings of Nurminskaya et al., Oliverio et al. and Hashimoto et al., alleging that such references strongly suggest to one of skill in the art the method of claims 11-13 (page 8-9 of the Office Action). Without acquiescing to the reasoning presented in the Office Action, Applicant has canceled claims 11-13 without prejudice or disclaimer, rendering the rejection moot.

In re Application of:  
Robert Terkeltaub  
Application No.: 10/669,540  
Filed: September 23, 2003  
Page 7

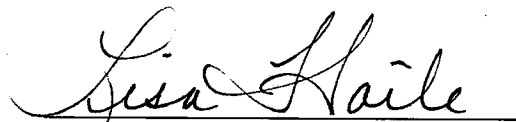
PATENT  
Attorney Docket No. UCSD1570-1

### Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

The Commissioner is hereby authorized to charge the total amount of \$65.00 for the One-Month Extension of Time fee, small entity, to Deposit Account No. 07-1896. No other fees are deemed necessary with the filing of this paper. However, the Commissioner is further authorized to charge any additional fees, or credit any overpayments, to Deposit Account No. 07-1896 referencing the above-identified docket number.

Respectfully submitted,



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